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Implementation, efficacy, and cost-effectiveness of the Unified Protocol in a Blended Format for the Transdiagnostic Treatment of Emotional Disorders: study protocol for a multicentre, randomized, superiority controlled trial in the Spanish National Health System

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Abstract

Introduction: Emotional disorders (EDs) have become the most prevalent psychological disorders in the general population, which has boosted the economic burden associated with their management. Approximately half of the individuals do not receive adequate treatment. Consequently, finding solutions to deliver cost-effective treatments for EDs has become a key goal of today's clinical psychology. Blended treatments, a combination of face-to-face and online interventions, have emerged as a potential solution to the previous. The Unified Protocol for the Transdiagnostic Treatment of EDs (UP) might serve this purpose, as it can be applied to a variety of disorders simultaneously and its manualized format makes it suitable for blended interventions.

Methods and analysis: The study is a multicentre, randomized, superiority, clinical trial. Participants will be 300 individuals with a diagnosis of an ED. They will be randomized to a treatment as usual (individual cognitive behavioral therapy) or a UP condition in a blended format (face to face individual UP + online, app-based UP). Primary outcomes will be ED diagnostic criteria and depression and anxiety symptoms. App usability, as well as opinion and confidence in the treatment will also be evaluated. Assessment points will include baseline and 3, 6 and 12 months after treatment onset.

Ethics and dissemination: The study has received the following approvals: Hospital Comarcal de Vinaròs (Reference 08/2019-05/2021), the USM La Milagrosa (Reference PI_2019/92), and Hospital Universitario Río Hortega (Reference 21-PI044). The study is currently under an approval process by the ethical and research committees of all the remaining collaborating centres. Outcomes will be disseminated through publication in peer-reviewed journals and presentations at international conference meetings.

Trial registration number: NCT04304911.

Keywords

Unified protocol, Transdiagnostic, Emotional disorders, Blended, Public health, Randomized Controlled trial (RCT).

Strengths and limitations of this study

- This study is the first RCT to test the efficacy, implementation, and cost-effectiveness of a transdiagnostic intervention in a blended format for the treatment of EDs in public settings in Spain.
- The blended UP may allow clinicians to use the same treatment for the most prevalent psychological disorders, that is, EDs.
- The blended UP can enable clinicians to use technology to motivate, monitor, give support, and provide treatment to patients without losing the benefits of individual face-to-face treatments.
- An UP-based treatment program in a blended format might help reduce dropouts and waiting lists because it allows clients to take advantage of the time between sessions, which might help them progress and engage with their treatments and therefore improve earlier and be discharged sooner.
- One limitation could be that some people may be resistant to participate in the blended condition due their thoughts being the app more impersonal and less effective.

INTRODUCTION

Emotional disorders (EDs; i.e., anxiety disorders, unipolar mood disorders, and related disorders) [1] are the most prevalent mental disorders in the general population [2]. In Spain, anxiety disorders and mood disorders affect approximately two million (4.1%) and two and half million (5.2%) individuals, respectively [3]. These disorders have a direct cost of 22.000 million euros (500 euros per capita and year) and the total expense of these disorders entails 2.2% of the Gross Domestic Product in Spain [4]. Due to the excessive demand for treatment, mental health services of our National Health System (NHS) are collapsed with large waiting lists, which results in a great difficulty to dedicate the recommended time to attend patients who require psychological treatment [4,5]. Therefore, there is an urgent need to find cost-effective solutions for the treatment of EDs in our NHS.

The Unified Protocol (UP) [6,7] is a structured, manualized transdiagnostic intervention for the treatment of EDs based on cognitive behavioral therapy (CBT). The UP aims to treat emotion regulation deficits, which are argued to be the underlying common factor in all EDs [8]. By focusing on these common mechanisms, the UP offers numerous

advantages. For example, it allows to simultaneously treat people with different EDs and comorbid presentations with a single protocol [9] and reduces the costs associated with training mental health professionals [10]. To date, three systematic reviews, which include two meta-analyses, have been conducted to summarize the efficacy of the UP. Overall, these studies reveal that the UP significantly improves anxious and depressive symptoms with moderate to large effect sizes. Additionally, the improvements appear to be maintained over time (up to 3 and 6 months of follow-up) [11-13]. In Spain, a previous clinical trial conducted in the NHS showed that the UP in a group format, compared with treatment as usual, achieved significantly larger improvements in anxious and depressive symptoms, as well as in quality of life at 6-month follow-up [14].

The preferred intervention format by patients with EDs attending the Spanish NHS is individual, face-to-face treatment (85.4%), followed by group (14.2%) and online interventions (0.4%) [15]. These results justify that blended treatments, which use online treatments but maintain some form of individual, face-to-face intervention, could be a potential solution to the availability problems of treatments for EDs in our Spanish NHS. The advantage of blended treatments is that they are dynamic and flexible because they allow using technology to motivate, monitor, give support, and treat patients. Importantly, this is done without losing face-to-face treatment sessions [16,17]. Research has shown that blended interventions are as effective as face-to-face treatments in the reduction of major depression [18] and anxiety symptoms [19]. A recent meta-analysis has also revealed optimistic results regarding the power of blended interventions, given that they may save time to the clinicians, in addition to decreasing dropouts and enhancing the maintenance of the benefits obtained w treatment over time [20].

The present study will compare the efficacy and cost-efficiency of the UP in a blended format against traditional, individual, unstructured CBT in a sample of patients with EDs. All the participants will seek treatment at the Spanish NHS. To ensure the generalizability of the results, our goal will be tested in several public mental health centres in Spain.

METHODS AND ANALYSIS

Study protocol

The current study is a superiority, multicentre, randomized controlled trial (RCT) with two active conditions: The UP in a blended format (individual UP face to face and UP-APP for Smartphone) and non-structured CBT in an individual format (treatment as usual, TAU).

The expected superiority comes from the fact that the participants in the blended condition will receive additional treatment compared with the TAU condition, which should enhance the benefits of the standard intervention. In the present investigation, all consecutive patients with EDs attending any of the collaborating centres (see "Sample and recruitment" section) will be asked to participate. It is important to note that this is a feasibility study in which the context and usual procedures of ED management will be kept as naturalistic as possible for implementation purposes. This means that there are some study characteristics that should be bared in mind. For example, some variables will not be predetermined and will only be known at the end of the investigation. This includes, for example, the frequency of the psychological appointments in both conditions (which will vary depending on the patient's evolution and clinician appraisals) or the time spent in the UP-APP by participants in the blended condition (i.e., amount of progress in the treatment modules and exercises). These variables, which might influence on outcomes, will of course be considered in the statistical analysis when the information is available (at the end of the study).

The study was registered on May 12, 2020 at https://clinicaltrials.gov/ (Trial NCT04304911). The flow chart of the study design is shown in Figure 1. A schedule of the enrolment, interventions, and assessments is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Table 1).

Sample size

To calculate the required sample size, we used the G*Power software [21]. We obtained a sample size of 129 participants per condition with a 95% power, an alpha coefficient of 0.01, and a conservative effect size of 0.30. Considering a dropout rate of 15%, we will recruit at least 150 participants per condition (N=300).

-Insert Fig. 1 around here-

Table 1. Study schedule of enrolment, interventions, and assessments

	STUDY PERIOD						
	Enrolment	**Pre-allocation**	**Allocation**	**Intervention**	**Post-allocation**		
TIMEPOINT	***-t1***	**t_0** Baseline	***t_1***	***t_2***	***t_3*** 3 months after the intervention	***t_4*** 6 months after the intervention	***t_5*** 12 months after the intervention
ENROLMENT:							
Eligibility screen	X						
MINI	X				X	X	X
Informed consent	X						
ALLOCATION:		X					
ODSIS		X		X	X	X	X
OASIS		X		X	X	X	X
INTERVENTIONS:							
Treatment as usual				←	- - - - -	- - - - -	→
UP in blended format				←	- - - - -	- - - - -	→
OTHER ASSESSMENTS:							
Demographics		X					
MEDI		X			X	X	X
EuroQol-5D		X			X	X	X
FFMQ		X			X	X	X
BEAQ		X			X	X	X
DERS		X			X	X	X
ERQ		X			X	X	X
SUS					X	X	X
TCS					X	X	X
CSRI					X	X	X
OTS					X	X	X
WAI-S				X			

QALYS	X	X	X	X

Note: *BEAQ,* Brief Experiential Avoidance Questionnaire; *CSRI,* Client Service Receipt Inventory; *CEQ*, Credibility/Expectancy Questionnaire; *DERS,* Difficulties in Emotion Regulation Scale; *ERQ,* Emotion Regulation Questionnaire*; FFMQ,* Five Factor Mindfulness Questionnaire *MEDI,* Multidimensional Emotional Disorder Inventory; *MINI,* Mini International Neuropsychiatric Interview; *OASIS,* Overall Anxiety Severity and Impairment Scale; *ODSIS,* Overall Depression Severity and Impairment Scale; QALYS, Quality-adjusted Life Years; SUS; System Usability Scale; *TOS*, Treatment Opinion Scale; *UP,* Unified Protocol for Transdiagnostic Treatment of Emotional Disorders*; WAI-S,* Working Alliance Inventory-Short

Procedure

UP-APP design (Patient and Public Involvement)

Prior to the design of the UP-APP, our team will conduct two different focus groups, one with patients who already received the UP for their EDs diagnosis and other with therapists trained in the UP intervention. Information about structure, content, format, design, exercises, language, duration, evaluation, feedback, security, adherence, usability, and customization will be collected in the focus groups. Besides, their opinion about the use of Apps and technological devices in clinical psychology and advantages and disadvantages of face-to-face therapy and app-based therapy will be also collected. Some researchers of the study and the engineer's team will participate in these focus groups as observers. The qualitative analysis of the data collected will be used to design the UP-APP for Smartphone.

Sample and recruitment

Participants are individuals over 18 years old, seeking psychological assistance in the Spanish Public Health System. Patients are referred to the study by licensed psychologists, psychiatrists, and clinical psychology residents working at the collaborating centres. Mental health professionals are responsible for assessing current DSM diagnoses (See "Measures" section) and the remaining eligibility criteria (see "Eligibility criteria" section). Individuals with comorbid diagnosis of several EDs are also enrolled in the study.

Recruitment is expected to start in January 2022. The study will be conducted in fifteen different mental health centres of the Spanish NHS, namely: USM Sagasta of Zaragoza, Hospital Comarcal de Vinaròs, Centro San Francisco Javier, USM La Milagrosa, Hospital Universitario Reina Sofía de Córdoba, CSM Eguía-Donostia, Hospital Universitario de

Alicante, CSM del Segrià, USM La Fuente de San Luís, USM Montoro de Córdoba, USM Tarazona, Hospital Universitario Río Hortega, USM Fraga, CSM Zafra, and CSM Mérida.

Elegibility criteria

Inclusion and exclusion criteria are described in Table 2.

Table 2. Eligibility criteria

Inclusion criteria	
1	Principal diagnosis of an emotional disorder[a]
2	The patient is over 18 years of age
3	The patient is fluent in the language in which the therapy is performed (Spanish in the present study)
4	The patient has a Smartphone (regardless of the condition, to ensure that the TAU condition does not include more patients that do not have access to a Smartphone)
5	Patients taking pharmacological treatment for their ED will be asked to maintain the same dosages and medications for at least 3 months prior to enrolling in the study and during the whole treatment[b]
6	The patient signs the informed consent form
Exclusion criteria	
1	The patient presents a severe condition that would require them to be prioritized for treatment. This includes a severe mental disorder (bipolar disorder, personality disorder, schizophrenia, or an organic mental disorder), suicide risk at the time of assessment, or substance use in the last three months
2	The patient has previously received 8 or more sessions of psychological treatment with clear and identifiable CBT principles within the past 5 years

[a]The following disorders will be included based on DSM-5 diagnostic criteria: major depression disorder, dysthymic disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, hypochondria, and adjustment disorders.
Patients with unspecified anxiety disorders and unspecified depressive disorders will also be included as they are frequent in public settings.
[b]If medication stability is not possible, the participant's data will be treated separately in the analyses

Randomization

All consecutive patients with a diagnosis of an ED attending any of the collaborating centres will be asked to participate in the present study. Once the inclusion criteria are met, every patient will be randomly assigned to one of the two experimental conditions: TAU or UP in a blended format. Patients who refuse to participate in the study will receive the TAU outside the RCT. This information will be recorded and reported in future studies once the trial has finished. Randomization will be performed by a researcher unrelated to the study using a computer-generated sequence (Randomizer). Randomization will be stratified according to the severity of the primary measures of depression and anxiety, using the recommended cut-off in the manuals. Stratification will be made to ensure a comparable proportion of severely depressed and anxious individuals in each group. For

each subgroup (i.e., severe or less severe depression and/or anxiety), participants will be randomly assigned to the UP in a blended format or to the TAU.

Therapists and interventions

Participants in both conditions will receive the individual therapy in a face-to-face format. The frequency of the appointment sessions with their clinicians will depend on the characteristics of their centres (e.g., existing waiting lists and availability of the clinicians). In addition to this individual face-to-face appointments, participants randomized to the blended condition will be able to use the UP-APP at any time and at whatever pace during the whole duration of the study. The clinicians will recommend the participants in the blended condition to work on modules 1, 2, 5, 6 and 8 during at least one week, and modules 3, 4 and 7 during at least two weeks (see the "Unified Protocol in a blended format" section for a detail on the titles of the UP modules).

The relatively naturalistic nature of this study prevents us to define, prior to the intervention, the exact number of sessions and the time spent in each psychological intervention (TAU vs. UP-blended). This also applies to the time spent by the participants in the UP-blended condition with the UP-APP. All these variables will be recorded by the UP-APP and the clinicians attending the participants for their inclusion in the statistical analyses.

For ethical reasons, if a patient feels uncomfortable with the blended format at any time during the study, they will receive the TAU outside the RCT.

Therapists participating in the study will include licensed psychologists with 8 to 20 years of experience in delivering CBT. All clinicians in the blended condition have been previously trained in the UP by a certified member of the research team (for more detail, see [23]).

Unified protocol in a blended format

For face-to-face interventions, the clinicians in this condition will follow the second edition of the UP therapist manual translated by Osma and Crespo into Spanish [24,25]. Between sessions, all participants in this condition will have access to the UP-APP. The APP includes the contents of the patient's manual, but using more dynamic and attractive digital material (videos and audios). The UP includes 8 modules: (1) Setting Goals & Maintaining Motivation; (2) Understanding Your Emotions; (3) Mindful Emotion

Awareness; (4) Cognitive Flexibility; (5) Countering Emotional Behaviors; (6) Facing Physical Sensations; (7) Emotion exposures, and (8) Moving UP from Here.

Treatment as usual (TAU)

This treatment condition will include individual, non-structured CBT. This is the treatment of choice by the psychologists at the collaborating Public Mental Health Centres. Individuals with an ED also frequently receive pharmacological treatment (i.e., antidepressants and / or anxiolytics), but this can only be prescribed by psychiatrists in Spain.

Measures

The evaluation protocol is administered by the therapists in a paper and pencil format at the participant's health centre or, when possible, through the Internet using the Qualtrics platform. The assessments will occur in 4 different time points: baseline, 3 months after starting the intervention (t_3), 6 months after starting the intervention (t_4), and 12 months after starting the intervention (t_5). Assessment instruments include demographic characteristics (age, sex, education, marital status, and work status), a diagnostic interview, and well-established questionnaires for both primary and secondary outcomes. At the end of the study, the clinicians in the TAU condition will complete a self-report sheet describing: the characteristics of their interventions using treatment modules as cues (psychoeducation module, identification of negative thoughts, breathing training, etc.), the average duration of sessions, the number of sessions delivered, the end-of-treatment date, and information on the number of appointments with the psychiatrist and pharmacological treatment prescribed during the study.

Information on the number of appointments with the psychiatrist and the pharmacological treatment prescribed during the study is also collected for patients in the blended condition following the same procedure described for the TAU condition.

Primary outcomes

We will administer the Overall Depression Severity and Impairment Scale (ODSIS) [26,27] and the Overall Anxiety Severity and Impairment Scale (OASIS) [27,28] weekly to assess the severity of depressive and anxiety symptoms, respectively. In addition to these symptoms, a principal diagnosis of EDs will be evaluated and monitored through

the study with the Mini-International Neuropsychiatric Interview (MINI) [29,30]. See Table 2 for more a chronologic detail of assessments.

Secondary outcomes

Our team is actually working on the Spanish validation of the Multidimensional Emotional Disorder Inventory (MEDI) [31]. In the present study, the Spanish version under the validation process will be used to evaluate the main transdiagnostic dimensions of EDs. Quality of life will be measured using the 5-itemEuroQol-5D [32,33]. Mindfulness will be assessed with the Five Facet Mindfulness Questionnaire (FFMQ) [34,35]. The questionnaire evaluates 5 components of mindfulness, namely observation, description, consciousness, non-judgment, and non-reactivity. Experiential avoidance will be measured with the Brief Experiential Avoidance Questionnaire (BEAQ) [36,37]. Emotion dysregulation will be evaluated with the Difficulties in Emotion Regulation Scale (DERS) [38,39], which presents five dysregulation dimensions: emotional lack of control, emotional rejection, life interference, lack of emotional attention, and emotional confusion. The Emotion Regulation Questionnaire (ERQ) [40,41] will also be used because it includes two important emotion regulation strategies, that is Cognitive Reappraisal and Expressive Suppression, of which the former is poorly represented in the DERS.

To assess implementation outcomes, we will evaluate the usability and the confidence in the treatment by means of the System Usability Scale (SUS) [42,43] and the Credibility/Expectancy Questionnaire (CEQ) [44,45], respectively. The Client Service Receipt Inventory (CSRI) [46,47] will be administered to evaluate the use of emergency services (number of visits), inpatient hospital admissions (number of days), and outpatient health care services (number of visits to the general practitioner, the nurse, the social worker, the psychologist, and other community health care professionals). For the cost-effectiveness analyses, we will use the Quality-adjusted Life Years (QALYs) [50,51] and the Client Service Receipt Inventory (CSRI) [46,47].

Finally, we will evaluate satisfaction outcomes in the patient. First, we will administer the Spanish short version of the Working Alliance Inventory [48,49], which evaluates the therapeutic or working alliance. Next, we will evaluate the patient's opinion of the intervention with the Treatment Opinion Scale (TOS). The TOS evaluates the quality of the intervention and its components, as well as the amount of discomfort experienced by

the patient during treatment. In the blended condition only, this measure will also evaluate the experience of participating in a blended format.

All measures used in the study have been validated in Spanish. Every administration time will take approximately 90 min considering the primary and the secondary outcomes altogether.

App Outcomes

App-related outcomes will include: number of logins, time of App use, number of completed modules and exercises, and amount of viewed videos. This information will be collected passively by the app without the need to ask the participant. An assessment based on the knowledge acquired in each module will also be conducted after completing every module. The App will also collect this information, including the correct/incorrect responses. The extent to which the participants consider that every module can help them to achieve their goals will be also registered after completing each module. Finally, a weekly assessment will be made to evaluate the evolution of the depression (ODSIS) [26,27] and the anxiety symptoms (OASIS) [27,28]. This weekly evaluation with the APP will also include the participants´ degree of motivation to continue working on the intervention.

Analyses

For the efficacy analyses, both completers and non-completers (intention-to-treat) analyses will be conducted separately. Then, a baseline comparison of both conditions in all study outcomes will be conducted to ensure that the randomization was successful. Next, mixed, multi-level, linear models will be conducted using the restricted maximum likelihood method to estimate the parameters. All the evaluations from all time points will be used in the models. The models will include covariates if baseline differences are detected. These analyses will be computed both for the primary and the secondary outcomes. The effect sizes will be computed and interpreted following the Cohen's proposal.

Missing data will be handled using a last-information carried forward approach when only one data point in the follow-up is missing, but mixed models, which can be conducted with missing data, will be implemented otherwise. For the remaining implementation outcomes (usability, acceptability, and satisfaction) we will compute

descriptive analyses. Implementation costs will be calculated by exploring the relationship between the cost of each intervention and its consequences in the form of QALYs, and by means of the interventions' penetration, that is, the number of consumers who were eligible or willing to use the app (end users). All analyses will be conducted with SPSS v24.0 [52] and Mplus v8.0 [53]. The study will follow the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) recommendations [54].

ETHICS

This study will be carried out in accordance with the study protocol, the Helsinki Declaration, and good clinical practice. This superiority, multicentre, RCT is currently under an approval process by the ethical and research committees of all the collaborating centres. It has already been approved by Hospital Comarcal de Vinaròs (Reference 08/2019-05/2021), USM La Milagrosa (Reference PI_2019/92), and Hospital Universitario Río Hortega (Reference 21-PI044).

Data handling will be carried out according to the premises established by Spanish laws [22]. The security and confidentiality of the participants' data are guaranteed by using alphanumeric codes (SUP001) instead of names. In addition, the demographic data will be hold separately from the rest of the data and will only be available to the researchers responsible for the data. The right to privacy will be a priority. The data obtained with the UP-APP will also comply with the mentioned guidelines. We will follow the necessary technical measures to ensure data safety and confidentiality, such as information encryption, access control and protection, security copies, updating of the operating system, security patches, centralized management of passwords, roles, users and privileges, patches management, and vulnerabilities detection. Outcomes will be disseminated through publication in peer-reviewed journals and presentations at international conference meetings. In addition, we will give visibility to the results through www.researchgate.net, https://clinicaltrials.gov/ and the website of our research group.

CONCLUSIONS

The present study may have important clinical implications because it is, to the best of our knowledge, the first RCT to test the efficacy, implementation, and cost-effectiveness of a transdiagnostic intervention in a blended format for the treatment of EDs in public

settings in Spain. Importantly, the results of this investigation will reveal whether the use of the UP in a blended format may serve to reduce existent waiting lists without decreasing the effectiveness of interventions. This would have important implications for patients and clinicians, as it would allow the former to take advantage of the time between sessions and would help them progress in their treatments thanks to the use of an app for Smartphone. This would, in turn, save time and costs in the latter.

Author contributions

JO: Conceptualization, funding acquisition, project administration, supervision, writing-original draft. LMG: Conceptualization, investigation, visualization, writing-original draft. OPB: Conceptualization, investigation, methodology, writing – review, and editing. MVNH: Conceptualization, writing - review and editing. AGP: Methodology, software, writing – review, and editing. CSR: Conceptualization, methodology, writing – review, and editing.

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Competing interests

None declared.

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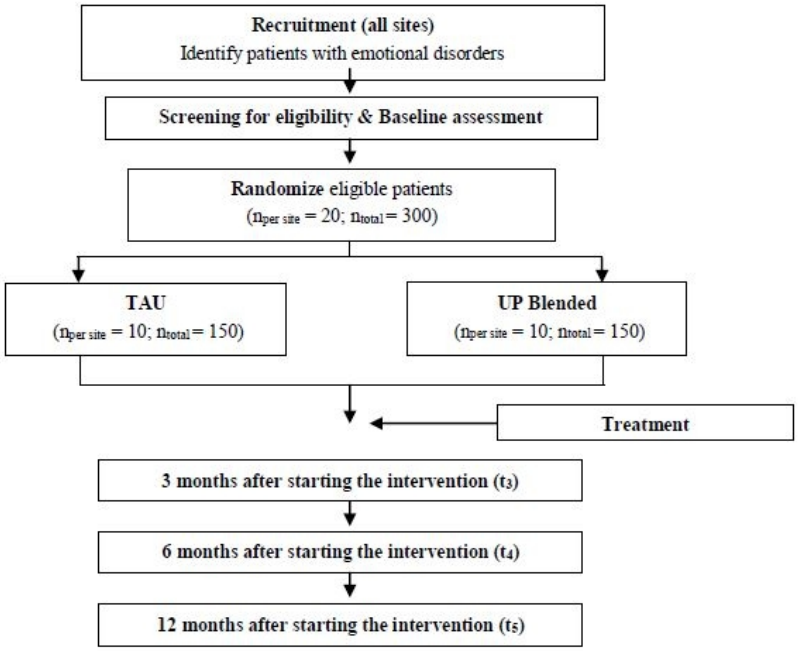

Flow Chart

187x134mm (96 x 96 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 4.
	2b	All items from the World Health Organization Trial Registration Data Set	Not reported
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	Tittle page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not Applicable
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2,3
	6b	Explanation for choice of comparators	2,3
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10, 11, 12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11, 12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not reported
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10, 11, 12

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12, 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12, 13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12, 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not applicable
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not reported
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not reported
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not reported
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Implementation, efficacy, and cost-effectiveness of the Unified Protocol in a Blended Format for the Transdiagnostic Treatment of Emotional Disorders: study protocol for a multicentre, randomized, superiority controlled trial in the Spanish National Health System

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Implementation, efficacy, and cost-effectiveness of the Unified Protocol in a Blended Format for the Transdiagnostic Treatment of Emotional Disorders: study protocol for a multicentre, randomized, superiority controlled trial in the Spanish National Health System

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Abstract

Introduction: Emotional disorders (EDs) have become the most prevalent psychological disorders in the general population, which has boosted the economic burden associated with their management. Approximately half of the individuals do not receive adequate treatment. Consequently, finding solutions to deliver cost-effective treatments for EDs has become a key goal of today's clinical psychology. Blended treatments, a combination of face-to-face and online interventions, have emerged as a potential solution to the previous. The Unified Protocol for the Transdiagnostic Treatment of EDs (UP) might serve this purpose, as it can be applied to a variety of disorders simultaneously and its manualized format makes it suitable for blended interventions.

Methods and analysis: The study is a multicentre, randomized, superiority, clinical trial. Participants will be 300 individuals with a diagnosis of an ED. They will be randomized to a treatment as usual (individual cognitive behavioral therapy) or a UP condition in a blended format (face to face individual UP + online, app-based UP). Primary outcomes will be ED diagnostic criteria and depression and anxiety symptoms. Cost-efficiency of the intervention, App usability, as well as opinion and confidence in the treatment will also be evaluated. Assessment points will include baseline and 3, 6 and 12 months after treatment onset.

Ethics and dissemination: The study has received the following approvals: blind note. The study is currently under an approval process by the ethical and research committees of all the remaining collaborating centres. Outcomes will be disseminated through publication in peer-reviewed journals and presentations at international conference meetings.

Trial registration number: blind

Keywords

Unified protocol, Transdiagnostic, Emotional disorders, Blended, Public mental health, Randomized Controlled trial (RCT).

Strengths and limitations of this study

- This study is the first RCT to test the efficacy, implementation, and cost-effectiveness of a transdiagnostic intervention in a blended format for the treatment of EDs in public settings in Spain.
- The blended UP may allow clinicians to use the same treatment for the most prevalent psychological disorders, that is, EDs.
- The blended UP can enable clinicians to use technology to motivate, monitor, give support, and provide treatment to patients without losing the benefits of individual face-to-face treatments.
- An UP-based treatment program in a blended format might help reduce dropouts and waiting lists because it allows clients to take advantage of the time between sessions, which might help them progress and engage with their treatments and therefore improve earlier and be discharged sooner.
- One limitation could be that some people may be resistant to participate in the blended condition because they perceive it as more impersonal and less effective

INTRODUCTION

Emotional disorders (EDs; i.e., anxiety disorders, unipolar mood disorders, and related disorders) [1] are the most prevalent mental disorders in the general population [2]. In Spain, anxiety disorders and mood disorders affect approximately two million (4.1%) and two and half million (5.2%) individuals, respectively [3]. These disorders have a direct cost of 22.000 million euros (500 euros per capita and year) and the total expense of these disorders entails 2.2% of the Gross Domestic Product in Spain [4]. Due to the excessive demand for treatment, mental health services of our National Health System (NHS) are overwhelmed with large waiting lists, which results in a great difficulty to dedicate the recommended time to attend patients who require psychological treatment [4,5]. Therefore, there is an urgent need to find cost-effective solutions for the treatment of EDs in our NHS.

The Unified Protocol (UP) [6,7] is a structured, manualized transdiagnostic intervention for the treatment of EDs based on cognitive behavioral therapy (CBT). The UP aims to treat emotion regulation deficits, which are argued to be the underlying common factor in all EDs [8]. By focusing on these common mechanisms, the UP offers numerous advantages. For example, it allows the simultaneous treatment of people with different

EDs and comorbid presentations with a single protocol [9] and reduces the costs associated with training mental health professionals [10]. To date, three systematic reviews, which include two meta-analyses, have been conducted to summarize the efficacy of the UP. Overall, these studies reveal that the UP significantly improves anxious and depressive symptoms with moderate to large effect sizes. Additionally, the improvements appear to be maintained over time (up to 3 and 6 months of follow-up) [11-13]. In Spain, a previous clinical trial conducted in the NHS showed that the UP in a group format, compared with treatment as usual, achieved significantly larger improvements in anxious and depressive symptoms, as well as in quality of life at 6-month follow-up [14].

The preferred intervention format by patients with EDs attending the Spanish NHS is individual, face-to-face treatment (85.4%), followed by group (14.2%) and online interventions (0.4%) [15]. These results justify that blended treatments, which use online treatments but maintain some form of individual, face-to-face intervention, could be a potential solution to the availability problems of treatments for EDs in our Spanish NHS. The advantage of blended treatments is that they are dynamic and flexible and they allow using technology to motivate, monitor, give support, and treat patients. Importantly, this is done without losing face-to-face treatment sessions [16,17]. Research has shown that blended interventions are more effective than face-to-face treatments in the reduction of depression and anxiety symptoms [18]. For example, one study found that a blended smartphone treatment, which consisted of four face-to-face sessions and a smartphone app to be used between the sessions, can be as effective as a full behavioural activation treatment in the reduction of major depression. Moreover, comparable scores were also obtained between the two conditions for treatment credibility and working alliance, and therapist time was reduced by an average of 47% in the blended condition [19]. Finally, a recent meta-analysis has also revealed optimistic results regarding the power of blended interventions, given that they allow saving time to the clinicians, in addition to decreasing dropouts and enhancing the maintenance of the benefits obtained with treatment over time [20].

The present study will compare the efficacy and cost-efficiency of the UP in a blended format against traditional, individual, unstructured CBT in a sample of patients with EDs. All the participants will seek treatment at the Spanish NHS. To ensure the generalizability

of the results, our outcomes will be evaluated in several public mental health centres in Spain.

METHODS AND ANALYSIS

Study protocol

The current study is a superiority, multicentre, randomized controlled trial (RCT) with two active conditions: The UP in a blended format (individual UP face to face and UP-APP for Smartphone) and non-structured CBT in an individual format (treatment as usual, TAU). The study is planned to start in January 2022 and end in December 2024.

The expected superiority comes from the fact that the participants in the blended condition will receive additional treatment compared with the TAU condition, which should enhance the benefits of the TAU. In the present investigation, all consecutive patients with EDs attending any of the collaborating centres (see "Sample and recruitment" section) will be asked to participate. It is important to note that this is a feasibility study in which the context and usual procedures of ED management will be kept as naturalistic as possible for implementation purposes. This means that there are some study characteristics that should be bared in mind. For example, some variables will not be predetermined and will only be known at the end of the investigation. This includes, for example, the frequency of the psychological appointments in both conditions (which will vary depending on the patient's evolution and clinician appraisals) or the time spent in the UP-APP by participants in the blended condition (i.e., amount of progress in the treatment modules and exercises). These variables, which might influence on outcomes, will of course be considered in the statistical analysis when the information is available (at the end of the study).

The study was registered on (blind note). The flow chart of the study design is shown in Figure 1. A schedule of the enrolment, interventions, and assessments is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Table 1).

Sample size

To calculate the required sample size, we used the G*Power software [21]. We obtained a sample size of 129 participants per condition with a 95% power, an alpha coefficient of 0.01, and a conservative effect size of 0.30. Considering a dropout rate of 15% and 5% of candidates who will not meet inclusion criteria, we will recruit at least 155 participants per condition (N=310). The expected effect size and dropout rates come from studies showing that blended interventions lead to lower dropout rates [20] and better outcomes in patients with anxiety and adjustment disorder [18] when compared to face-to-face interventions.

-Insert Fig. 1 around here-

Table 1. Study schedule of enrolment, interventions, and assessments

	STUDY PERIOD						
	Enrolment	**Pre-allocation**	**Allocation**	**Intervention**	**Post-allocation**		
TIMEPOINT	***-t1***	**t_0** **Baseline**	***t_1***	***t_2***	***t_3*** **3 months after the intervention**	***t_4*** **6 months after the intervention**	***t_5*** **12 months after the intervention**
ENROLMENT:							
Eligibility screen	X						
MINI	X				X	X	X
Informed consent	X						
ALLOCATION:		X					
ODSIS		X		X	X	X	X
OASIS		X		X	X	X	X
INTERVENTIONS:							
Treatment as usual				←---→			
UP in blended format				←---→			
OTHER ASSESSMENTS:							
Demographics		X					
MEDI		X			X	X	X
EuroQol-5D		X			X	X	X
FFMQ		X			X	X	X

BEAQ	X			X	X	X
DERS	X			X	X	X
ERQ	X			X	X	X
SUS				X	X	X
CEQ				X	X	X
CSRI				X	X	X
OTS				X	X	X
WAI-S			X			
QALYS	X			X	X	X

Note: *BEAQ,* Brief Experiential Avoidance Questionnaire; *CSRI,* Client Service Receipt Inventory; *CEQ*, Credibility/Expectancy Questionnaire; *DERS,* Difficulties in Emotion Regulation Scale; *ERQ,* Emotion Regulation Questionnaire*; FFMQ,* Five Factor Mindfulness Questionnaire *MEDI,* Multidimensional Emotional Disorder Inventory; *MINI,* Mini International Neuropsychiatric Interview; *OASIS,* Overall Anxiety Severity and Impairment Scale; *ODSIS,* Overall Depression Severity and Impairment Scale; QALYS, Quality-adjusted Life Years; SUS; System Usability Scale; *TOS*, Treatment Opinion Scale; *UP,* Unified Protocol for Transdiagnostic Treatment of Emotional Disorders*; WAI-S,* Working Alliance Inventory-Short

Procedure

UP-APP design (Patient and Public Involvement)

Prior to the design of the UP-APP, our team will conduct two different focus groups, one with patients who already received the UP for their EDs diagnosis and other with therapists trained in the UP intervention. Information about structure, content, format, design, exercises, language, duration, evaluation, feedback, security, adherence, usability, and customization will be collected in the focus groups. Besides, their opinion about the use of Apps and technological devices in clinical psychology and advantages and disadvantages of face-to-face therapy and app-based therapy will be also collected. Some researchers of the study and the engineer's team will participate in these focus groups as observers. The focus groups will be recorded on video to be transcribed by two researchers of the study. The qualitative analysis of the data collected will be used to design the UP-APP for Smartphone. This analysis will consist of generating a system of codes, grouping the he information provided by the participants in the focus groups that referred to the same ideas or highlighting the main ideas.

Sample and recruitment

Participants are individuals over 18 years old, seeking psychological assistance in the Spanish Public Health System. Patients are referred to the study by licensed psychologists, psychiatrists, and clinical psychology residents working at the collaborating centres. Mental health professionals (therapists and psychiatrists from the units to which patients are referred to and who want to collaborate in the study) will be responsible for assessing the current DSM diagnoses (See "Measures" section) and the remaining eligibility criteria (see "Eligibility criteria" section). Individuals with comorbid diagnosis of several EDs are also enrolled in the study.

Recruitment is expected to start in January 2022. The study will be conducted in fifteen different mental health centres of the Spanish NHS, namely: blind note.

Elegibility criteria

Inclusion and exclusion criteria are described in Table 2.

Table 2. Eligibility criteria

Inclusion criteria	
1	Principal diagnosis of an emotional disorder[a]
2	The patient is over 18 years of age
3	The patient is fluent in the language in which the therapy is performed (Spanish in the present study)
4	The patient has a Smartphone (regardless of the condition, to ensure that the TAU condition does not include more patients that do not have access to a Smartphone)
5	Patients taking pharmacological treatment for their ED will be asked to maintain the same dosages and medications for at least 3 months prior to enrolling in the study and during the whole treatment[b]
6	The patient signs the informed consent form (supplementary file)
Exclusion criteria	
1	The patient presents a severe condition that would require them to be prioritized for treatment. This includes a severe mental disorder (bipolar disorder, personality disorder, schizophrenia, or an organic mental disorder), suicide risk at the time of assessment, or substance use in the last three months
2	The patient has previously received 8 or more sessions of psychological treatment with clear and identifiable CBT principles within the past 5 years

[a]The following disorders will be included based on DSM-5 diagnostic criteria: major depression disorder, dysthymic disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, hypochondria, and adjustment disorders.
Patients with unspecified anxiety disorders and unspecified depressive disorders will also be included as they are frequent in public settings.
[b]If medication stability is not possible, the participant's data will be treated separately in the analyses

Randomization

All consecutive patients with a diagnosis of an ED attending any of the collaborating centres will be asked to participate in the present study. Once the inclusion criteria are met, every patient will be randomly assigned to one of the two experimental conditions:

TAU or UP in a blended format. Patients who refuse to participate in the study will receive the TAU outside the RCT. The number of people refusing to participate and the reasons for that decision will be recorded and reported due its interest for future studies. Randomization will be performed by a researcher unrelated to the study using a computer-generated sequence (Randomizer). Randomization will be stratified according to the severity of the primary measures of depression and anxiety, using the cut-off reported in Spanish clinical samples of ED, which has been 10 (0-20) in both scales [22]. This cut-off differentiates patients with moderate-severe symptoms from those with moderate-low symptoms.

Stratification will be made to ensure a comparable proportion of severely depressed and anxious individuals in each group. For each subgroup (i.e., severe or less severe depression and/or anxiety), participants will be randomly assigned to the UP in a blended format or to the TAU.

Therapists and interventions

Participants in both conditions will receive the individual therapy in a face-to-face format. Individuals with an ED also frequently receive pharmacological treatment (i.e., antidepressants and / or anxiolytics) as treatment of choice in the Spanish Mental Health System. The frequency of the appointment sessions with their clinicians will depend on the characteristics of their centres (e.g., existing waiting lists and availability of the clinicians). In addition to these individual face-to-face appointments, participants randomized to the blended condition will be able to use the UP-APP at any time and at whatever pace during the whole duration of the study. Clinicians will recommend participants in the blended condition to work on modules 1, 2, 5, 6 and 8 during at least one week, and modules 3, 4 and 7 during at least two weeks (see the "Unified Protocol in a blended format" section for a detail on the titles of the UP modules).

The relatively naturalistic nature of this study prevents us from defining, prior to the intervention, the exact number of sessions and the time spent in each psychological intervention (TAU vs. UP-blended). This also applies to the time spent by the participants in the UP-blended condition with the UP-APP. All these variables will be recorded by the UP-APP and the clinicians attending the participants for their inclusion in the statistical analyses.

Previous to start the RCT we will conduct an open pilot study to analyze the preliminary data of the clinical utility and feasibility of the UP-APP in a small sample of patients with emotional disorders diagnosis. Specifically, after the clinical assessment, from those who met the inclusion and exclusion criteria, we will invite 10 patients (in order of date of receipt) to participate voluntarily in this pilot study. Participants will sign the informed consent and data protection. Then, they will be randomized to one baseline condition: 1, 2 and 3 weeks in order of date of receipt (baseline measures will be ODSIS and OASIS [22]). Then patients will receive a face-to-face psychological treatment in a blended format and will receive the instructions to download the UP-APP in their Smartphone. They will be asked to complete a special set of questions to assess the comprehension, appearance, utility, interest, if they would recommend it to other people, usability, intention to use in the future, and satisfaction of the contents of each module of the UP-APP (ad hoc).

For ethical reasons, if a patient feels uncomfortable with the blended format at any time during the study, they will receive the TAU outside the RCT.

Therapists participating in the study will include licensed psychologists with 8 to 20 years of experience in delivering CBT.

Unified protocol in a blended format

For face-to-face interventions, the clinicians in this condition will follow the second edition of the UP therapist manual translated by Osma and Crespo into Spanish [23,24]. Therapists in the UP group received a training workshop on UP prior to the start of the intervention. This consisted of 2 or 3 group workshop sessions in which the therapists were instructed on the delivery of the different UP treatment modules. The duration of the course was between 10 and 20 hours, depending on the availability of the therapists at the centre. In addition to the workshop, all therapists received individual training during 12 therapy sessions. The individual training consisted of either online supervision before each session or participation as a co-therapist with an expert in the implementation of the UP intervention, who also evaluates the fidelity of the treatment. In both cases, the training was led by the lead author (blind note), who has been certified as a UP Trainer by the Unified Protocol Institute.

Between sessions, all participants in this condition will have access to the UP-APP. The APP includes the contents of the patient's manual, but using more dynamic and attractive

digital material (videos and audios). The UP includes 8 modules: (1) Setting Goals & Maintaining Motivation; (2) Understanding Your Emotions; (3) Mindful Emotion Awareness; (4) Cognitive Flexibility; (5) Countering Emotional Behaviors; (6) Facing Physical Sensations; (7) Emotion exposures, and (8) Moving UP from Here.

In the UP-APP, after completing each module, an assessment of the knowledge acquired will be carried out using true/false questions. The App will collect the correct/incorrect responses and will provide feedback to the participants. Thus, participants will receive positive reinforcement as they progress through the modules and get correct answers to keep them engaged and motivated in the use of the App. In addition, participants will have to complete different exercises throughout the modules, such as records or activities to identify emotion-driven behaviours. They will also be provided with examples of real patients with whom they can identify and which will help them to complete their records. Finally, a weekly assessment will be made to evaluate the evolution of the depression and the anxiety symptoms (ODSIS and OASIS) [22]. The scores over time will be shown to the participants with a graphic display. This weekly evaluation with the APP will also include the participants´ degree of motivation to continue working on the intervention.

Treatment as usual (TAU)

This treatment condition will include individual, non-structured CBT using the following techniques: Psychoeducation, cognitive restructuring, relaxation techniques, mindfulness techniques, exposure techniques, activity scheduling, problem solving and training in communication techniques. This is the treatment of choice by the psychologists at the collaborating Public Mental Health Centres.

Measures

The evaluation protocol is administered by the therapists in a paper and pencil format at the participant's health centre or, when possible, through the Internet using the Qualtrics platform. The assessments will occur in 4 different time points: baseline, 3 months after starting the intervention (t_3), 6 months after starting the intervention (t_4), and 12 months after starting the intervention (t_5). Assessment instruments include demographic characteristics (age, sex, education, marital status, and work status), a diagnostic interview, and well-established questionnaires for both primary and secondary outcomes.

At the end of the study, the clinicians in the TAU condition will complete a self-report sheet describing: the characteristics of their interventions using treatment modules as cues (psychoeducation module, identification of negative thoughts, breathing training, etc.), the average duration of sessions, the number of sessions delivered, the end-of-treatment date, and information on the number of appointments with the psychiatrist and pharmacological treatment prescribed during the study.

Information on the number of appointments with the psychiatrist and the pharmacological treatment prescribed during the study is also collected for patients in the blended condition following the same procedure described for the TAU condition. All the participants using the UP-App will be informed about the data that is going to be registered while using it. Primary and secondary outcomes are described in Table 3.

Table 3. Clinical Outcomes

Instrument	Construct	Reliability (α)	Response range
Primary outcomes			
ODSIS [22,25]	Severity of depressive symptoms	.94	5-point Likert scale ranging from 0 (I didn't feel depressed) to 4 (Constant depression)
OASIS [22,26]	Severity of anxiety symptoms	.87	5-point Likert scale ranging from 0 (I didn't feel anxious) to 4 (Constant anxiety)
MINI [27,28]	Principal diagnosis of ED	NA	Structured diagnostic interview
Secondary outcomes			
		Patient Outcomes	
MEDI [29]	Transdiagnostic dimensions of ED's	NA	9-point Likert response scale ranging from 0 (not characteristic of me/does not apply to me) to 8 (extremely characteristic of me/applies to me very much)
EuroQol-5D [30,31]	Quality of life	NA	5 items ranging from 1 (I do not have problems) to 3 (unable to perform these activities). Thermometer from 0 (worst imaginable health status) to 100 (best imaginable health status)
FFMQ [32,33]	Mindfulness dimensions	.80 to .91	Likert scale ranging from 1 (never or very rarely true) to 5 (very often or always true)
BEAQ [34,35]	Experiential avoidance	.82	6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree)
DERS [36,37]	Emotion regulation	.73 to .93	5-point Likert scale ranging from 1 (never or very rarely) to 5 (very often or always)
ERQ [38,39]	Cognitive Reappraisal and Expressive Suppression		7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree).
		Implementation Outcomes	
SUS [40,41]	Usability	.81	5-point Likert scale ranging from 1 (strong disagreement) to 5 (strong agreement).
CEQ [42,43]	Confidence in the treatment (credibility and client expectancy)	.85	9-point scale rated from 1 (not at all confident) to 9 (very confident).
CSRI [44,45]	Emergency service (total visits), general medical	NA	NA

	inpatient hospital admissions (total days) and outpatient health care services (total visits)		
QALYS [46,47]	Quality-adjusted Life Years	NA	NA
		Patient Satisfaction Outcomes	
WAI-S [48,49]	Working alliance	.91	7-point Likert scale ranging from 1 (never) to 7 (always)
TOS (ad hoc)	Quality of the intervention and its components, discomfort experienced during treatment and the experience of participating in a blended format	NA	4-point Likert scale ranging from 0 (poor or nothing) to 3 (excellent or very much) and 11-point response scale in some items ranging from 0 (nothing) to 10 (very much).
		App Outcomes	
App	Time of use of the App, videos viewed and exercises completed.	NA	NA

Note: BEAQ: Brief Experiential Avoidance Questionnaire; CEQ: Credibility/Expectancy Questionnaire; CSRI: Client Service Receipt Inventory; DERS: Difficulties in Emotion Regulation Scale; ED: Emotional Disorder; ERQ: Emotion Regulation Questionnaire; FFMQ: Five Facet Mindfulness Questionnaire; MEDI: Multidimensional Emotional Disorder Inventory; MINI: Mini-International Neuropsychiatric Interview; NA: Not Applicable; OASIS: Overall Anxiety Severity and Impairment Scale; ODSIS: Overall Depression Severity and Impairment Scale; SUS: The System Usability Scale; TOS: Treatment Opinion Scale.
Scale reliability corresponds to the Cronbach's alpha coefficient *p < .01 **p < .001.

Analyses

For the efficacy analyses, both completers and non-completers (intention-to-treat) analyses will be conducted separately. Then, a baseline comparison of both conditions in all study outcomes will be conducted to ensure that the randomization was successful. Next, mixed, multi-level, linear models will be conducted using the restricted maximum likelihood method to estimate the parameters. All the evaluations from all time points will be used in the models. The models will include covariates if baseline differences are detected. Specifically, the linear mixed model analysis will include the main effects of time (each variable collected at each evaluation time to analyze the evolution over time). The treatment condition and the number of sessions will also be included as interaction effects with time (in order to see differences in the evolution of the variables as a function of the treatment condition and/or as a function of the number of sessions). Finally, the center where the participants have received the treatment will be included as random effects in the model. These analyses will be computed both for the primary and the secondary outcomes. The effect sizes will be computed and interpreted following the Cohen's proposal. Additionally, we will also calculate the Reliable Change Index (RCI) and the Reliable Recovery Index (RRI) to evaluate the effectiveness of both interventions, as proposed by Jacobson and Truax [50].

Missing data will be handled using mixed models, which can be conducted with missing data [51]. For the remaining implementation outcomes (usability, acceptability, and satisfaction) we will compute descriptive analyses. Cost-effectiveness will be calculated by exploring the relationship between the cost of each intervention (cost of TAU or UP in a blended format, number of sessions, medication and use of health resources carried out by the participants [evaluated through the CSRI]) and its consequences in the form of QALYs (standardized health units that allow the quantification of individuals' preferences regarding the quality of life that has been produced by a health intervention [52], the information obtained through the Euroqol allows the calculation of QALYs). Other measures of intervention penetration will be used, such as the number of consumers who were eligible or willing to use the app (end users). All analyses will be conducted with SPSS v24.0 [53] and Mplus v8.0 [54]. The study will follow the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) recommendations [55].

ETHICS

This study will be carried out in accordance with the study protocol, the Helsinki Declaration, and good clinical practice. This superiority, multicentre, RCT is currently under an approval process by the ethical and research committees of all the collaborating centres. It has already been approved by (blind note).

Data handling will be carried out according to the premises established by Spanish laws [56]. The security and confidentiality of the participants' data are guaranteed by using alphanumeric codes (SUP001) instead of names. In addition, the demographic data will be hold separately from the rest of the data and will only be available to the researchers responsible for the data. The right to privacy will be a priority. The data obtained with the UP-APP will also comply with the mentioned guidelines. We will follow the necessary technical measures to ensure data safety and confidentiality, such as information encryption, access control and protection, security copies, updating of the operating system, security patches, centralized management of passwords, roles, users and privileges, patches management, and vulnerabilities detection. Outcomes will be disseminated through publication in peer-reviewed journals and presentations at international conference meetings. In addition, we will give visibility to the results through www.researchgate.net, https://clinicaltrials.gov/ and the website of our research group.

Author contributions

JO: Conceptualization, funding acquisition, project administration, supervision, writing-original draft. LMG: Conceptualization, investigation, visualization, writing-original draft. OPB: Conceptualization, investigation, methodology, writing – review, and editing. MVNH: Conceptualization, writing - review and editing. AGP: Methodology, software, writing – review, and editing. CSR: Conceptualization, methodology, writing – review, and editing.

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Competing interests

None declared.

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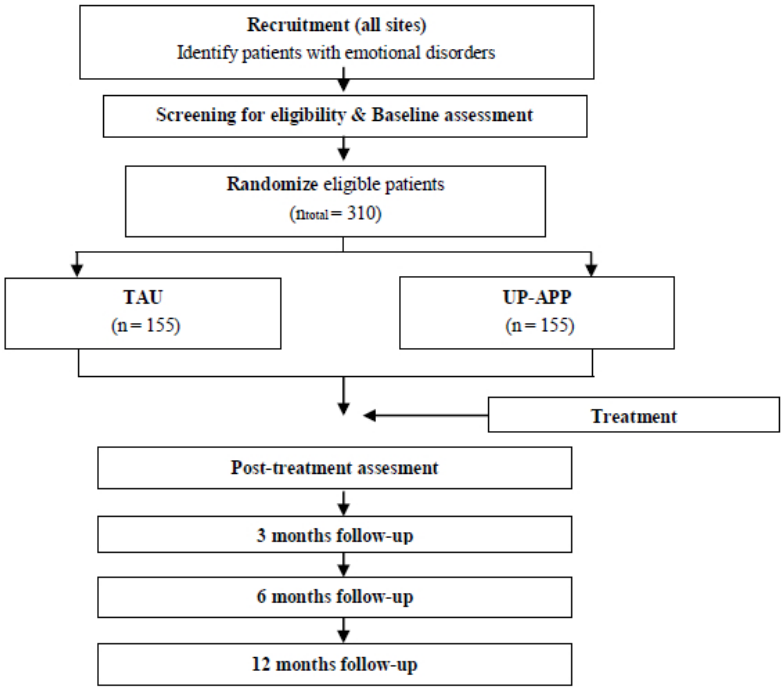
Fig. 1 Study flow chart



Study flow chart

482x389mm (38 x 38 DPI)

Supplementary material. Patient Informed Consent

PATIENT INFORMED CONSENT

PROJECT TITLE: Study of the implementation, efficacy and cost-effectiveness of the Unified Protocol in hybrid format for the transdiagnostic treatment of emotional disorders in the Spanish NHS (PI20/00697)

PRINCIPAL INVESTIGATOR: <<name and surname of the principal investigator>>

Centre/Hospital: <<name of the Mental Health Centre>>

FUNDING ENTITY: Study funded by the Ministry of Science and Innovation, Instituto de Salud Carlos III for Health Research Projects of the 2020 call of the Strategic Action in Health 2017-2020 (code PI20/00697).

GENERAL DESCRIPTION: We are writing to inform you about a research study in which you are invited to participate and which has been approved by the <<name of the Drug Research Ethics Committee of the Hospital>>. Considering that you suffer from an Emotional Disorder (mood or anxiety disorder), we are asking for your consent to participate in a study about which we inform you below. Before deciding whether or not you want to participate, please read this document carefully, which includes information about this project. You can ask any questions you may have and ask for clarification on any aspect of the study.

PURPOSE OF THE STUDY: We are contacting you to request your collaboration in the research project entitled: "Study of implementation, efficacy and cost-effectiveness of the Unified Protocol in hybrid format for the transdiagnostic treatment of emotional disorders in the Spanish NHS". Our objective with this research is to analyse the efficacy and cost-effectiveness of a transdiagnostic psychological treatment applied in a hybrid format (face-to-face treatment + mobile App), with the aim of providing a resource that allows working and training skills in the period between face-to-face appointments. To do this, a randomly selected group of users of a Mental Health Unit will receive the usual psychological treatment at the centre, and another group will receive the treatment in hybrid format (face-to-face treatment + mobile App).

EXPLANATION OF THE STUDY: Through a randomisation system, participants will be assigned to one or other of the following treatment modalities:

- Usual psychological treatment modality of the centre (individual and face-to-face format).
- Hybrid treatment modality (individual and face-to-face treatment + mobile App).

Study activities - Usual psychological treatment condition of the centre

The following is the procedure and activities that you will carry out in this treatment modality:

1. An initial psychological assessment will be carried out (by means of structured diagnostic clinical interview). The results of the assessment will be part of a database of participants. The estimated duration is between 20-30 minutes.

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2. Pre-intervention assessment: Before starting the psychological intervention, you will have to complete the full assessment protocol. This consists of a series of questionnaires and is estimated to take between 30-45 minutes to complete.
3. Usual treatment: Psychological intervention following the usual treatment used in your health centre. You will have a psychologist assigned to you from your Mental Health Centre, who will be in charge of making individual appointments and offering you the psychological treatment he/she considers appropriate according to your psychological needs.
4. Follow-up evaluations at 3, 6 and 12 months after starting the intervention: the complete evaluation protocol will be administered again during the follow-ups that will take place at 3, 6 and 12 months after starting the psychological intervention (estimated duration to fill them in is between 30-45 minutes).

Study activities - Hybrid treatment condition (individual and face-to-face treatment + mobile App).

Below, we present the procedure and activities that you will carry out in the event that you agree to participate in this project and are assigned through the randomisation system to the hybrid treatment condition (face-to-face treatment + mobile App):

5. An initial psychological assessment (by means of a structured clinical diagnostic interview) will be carried out. The results of the assessment will be part of a database of participants. The estimated duration is between 20-30 minutes.
6. Pre-intervention assessment: Before starting the psychological intervention, you will complete the full assessment protocol consisting of a series of questionnaires, estimated to take between 30-45 minutes to complete.
7. Psychological Treatment based on the Unified Protocol + App: Transdiagnostic cognitive-behavioural treatment applied in a hybrid format (face-to-face treatment + App). To ensure that all participants receive the same intervention, therapists will use the Unified Protocol Manual (Barlow et al., 2018a). This Protocol consists of 8 treatment modules (Table 2). The duration and frequency of individual sessions will be determined by the clinical psychologist according to their availability and schedule. The treatment modules content is shown in Table 2.

Table 2. Treatment modules and content

Module 1	Setting Goals & Maintaining Motivation
Module 2	Understanding your emotions
Module 3	Mindful Emotion Awareness
Module 4	Cognitive flexibility
Module 5	Countering Emotional Behaviors
Module 6	Facing Physical Sensations
Module 7	Emotion exposures

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Module 8	Moving UP from here

8. Follow-up assessments at 3, 6 and 12 months after starting the intervention: the complete assessment protocol will be administered again during the follow-ups that will take place 3, 6 and 12 months after starting the psychological intervention (estimated time to complete them is between 30-45 minutes).

RISKS AND DISCOMFORTS OF PARTICIPATING IN THE STUDY

Both treatment modalities have demonstrated their efficacy and the benefit to be obtained with this study is to improve the efficiency of psychological treatments for the treatment of people with emotional disorders. In addition, there are no risks associated with participation in this research.

BENEFIT AND MEDICAL CARE

It is likely that you will not receive any personal benefit from your participation in this study. However, the data collected in this study may lead to increased knowledge about emotional disorders.

VOLUNTARY PARTICIPATION

Your participation in this study is completely voluntary: If you decide not to participate, you will receive all the medical care you may need and your relationship with the medical team caring for you will not be affected.

DATA PROCESSING AND CONFIDENTIALITY

Your consent is requested for the use of your data for the development of this project. Both personal data (age, sex, race) and health data will be collected using a coding procedure. Only your therapist and the main researcher at the centre, will be able to relate this data to you, being responsible for keeping all data you provide. The information will be processed during the analysis of the results obtained and will appear in the final reports. In no case will it be possible to identify you, guaranteeing the confidentiality of the information obtained, in compliance with current legislation.

The study complies with the provisions of Organic Law 3/2018, of 5 December, on the protection of personal data and the guarantee of digital rights, which repeals Organic Law 15/1999, of 5 December, on the protection of personal data. Also complies with the European Parliament Regulation 2016/679 of personal data protection, the Helsinki Declaration (Seul, 2008) and the Biomedic Research Law 14/2007.

Personal data will be processed by <<name and surname of the principal investigator>>. No data will be passed on to third parties, unless legally obliged to do so. You will be informed that you have the right to access, rectify, delete, limit or oppose the processing of your data.

Access to your identified personal information will be restricted to the study doctor/collaborators, health authorities (Spanish Agency of Medicines and Health Products, foreign health authorities), the Research Ethics Committee and personnel authorised by the sponsor (study monitors, auditors), when required to check the study data and procedures, but always maintaining their confidentiality in accordance with current legislation.

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The data will be collected in a research file under the responsibility of the institution and will be processed in the framework of its participation in this study.

The promoter will adopt the appropriate measures to guarantee the protection of your privacy and will not allow your data to be cross-referenced with other databases that could allow you to be identified.

In accordance with data protection legislation, you may exercise your rights of access, modification, objection and deletion of data by contacting your psychologist.

REVOCATION OF CONSENT

You may revoke your participation at any time without explanation. In this case, no new data will be collected after you leave the study.

If you have any questions you can ask your psychologist now or later, even after the study has begun. If you wish to ask questions later, you can contact the person in charge of the research: blind note

Thank you very much for your attention.

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INFORMED CONSENT FORM

PROJECT TITLE: Study of the implementation, efficacy and cost-effectiveness of the Unified Protocol in hybrid format for the transdiagnostic treatment of emotional disorders in the Spanish NHS (PI20/00697)

PRINCIPAL INVESTIGATOR: <<name and surname of the principal investigator>>

Centre/Hospital: <<name of the Mental Health Centre>>

FUNDING ENTITY: Study funded by the Ministry of Science and Innovation, Instituto de Salud Carlos III for Health Research Projects of the 2020 call of the Strategic Action in Health 2017-2020 (code PI20/00697).

I, <<name and surname of the participant>>

□ I have read the information sheet I have been given about the study.

□ I have been able to ask questions about the study.

□ I have received sufficient information about the study.

□ I have spoken to <<name and surname of the Psychologist>>.

□ I understand that my participation is voluntary.

□ I understand that I can withdraw from the study:

- Whenever I want.
- Without having to explain myself.
- Without affecting my medical care.

I will receive a signed and dated copy of this informed consent document.

I freely give my agreement to participate in the study.

Signature of the legal representative, family member or de facto related person	Signature of the researcher/Psychologists

Date:

I wish to be informed of information derived from the research that may be relevant to my health:

☐ YES

☐ NO

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 4.
	2b	All items from the World Health Organization Trial Registration Data Set	Not reported
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	Tittle page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not Applicable
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2,3
	6b	Explanation for choice of comparators	2,3
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10, 11, 12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11, 12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not reported
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10, 11, 12

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12, 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12, 13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12, 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not applicable
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not reported
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not reported
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not reported
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Implementation, efficacy, and cost-effectiveness of the Unified Protocol in a Blended Format for the Transdiagnostic Treatment of Emotional Disorders: study protocol for a multicentre, randomized, superiority controlled trial in the Spanish National Health System

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Evidence based practice, Mental health
Keywords:	Anxiety disorders < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, PUBLIC HEALTH, MENTAL HEALTH

Implementation, efficacy, and cost-effectiveness of the Unified Protocol in a Blended Format for the Transdiagnostic Treatment of Emotional Disorders: study protocol for a multicentre, randomized, superiority controlled trial in the Spanish National Health System

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Abstract

Introduction: Emotional disorders (EDs) have become the most prevalent psychological disorders in the general population, which has boosted the economic burden associated with their management. Approximately half of the individuals do not receive adequate treatment. Consequently, finding solutions to deliver cost-effective treatments for EDs has become a key goal of today's clinical psychology. Blended treatments, a combination of face-to-face and online interventions, have emerged as a potential solution to the previous. The Unified Protocol for the Transdiagnostic Treatment of EDs (UP) might serve this purpose, as it can be applied to a variety of disorders simultaneously and its manualized format makes it suitable for blended interventions.

Methods and analysis: The study is a multicentre, randomized, superiority, clinical trial. Participants will be 300 individuals with a diagnosis of an ED. They will be randomized to a treatment as usual (individual cognitive behavioral therapy) or a UP condition in a blended format (face to face individual UP + online, app-based UP). Primary outcomes will be ED diagnostic criteria and depression and anxiety symptoms. Cost-efficiency of the intervention, App usability, as well as opinion and confidence in the treatment will also be evaluated. Assessment points will include baseline and 3, 6 and 12 months after treatment onset.

Ethics and dissemination: The study has received the following approvals: Ethics Research Committee of Navarra, Castellón, Euskadi, Castilla y León, Extremadura, Lleida and Aragón. The study is currently under an approval process by the Ethics Research Committees of all the remaining collaborating centres. Outcomes will be disseminated through publication in peer-reviewed journals and presentations at international conference meetings.

Trial registration number: NCT04304911

Keywords

Unified protocol, Transdiagnostic, Emotional disorders, Blended, Public mental health, Randomized Controlled trial (RCT).

Strengths and limitations of this study

- This study is the first RCT to test the efficacy, implementation, and cost-effectiveness of a transdiagnostic intervention in a blended format for the treatment of EDs in public settings in Spain.
- The blended UP may allow clinicians to use the same treatment for the most prevalent psychological disorders, that is, EDs.
- The blended UP can enable clinicians to use technology to motivate, monitor, give support, and provide treatment to patients without losing the benefits of individual face-to-face treatments.
- An UP-based treatment program in a blended format might help reduce dropouts and waiting lists because it allows clients to take advantage of the time between sessions, which might help them progress and engage with their treatments and therefore improve earlier and be discharged sooner.
- One limitation could be that some people may be resistant to participate in the blended condition because they perceive it as more impersonal and less effective

INTRODUCTION

Emotional disorders (EDs; i.e., anxiety disorders, unipolar mood disorders, and related disorders) [1] are the most prevalent mental disorders in the general population [2]. In Spain, anxiety disorders and mood disorders affect approximately two million (4.1%) and two and half million (5.2%) individuals, respectively [3]. These disorders have a direct cost of 22.000 million euros (500 euros per capita and year) and the total expense of these disorders entails 2.2% of the Gross Domestic Product in Spain [4]. Due to the excessive demand for treatment, mental health services of our National Health System (NHS) are overwhelmed with large waiting lists, which results in a great difficulty to dedicate the recommended time to attend patients who require psychological treatment [4,5]. Therefore, there is an urgent need to find cost-effective solutions for the treatment of EDs in our NHS.

The Unified Protocol (UP) [6,7] is a structured, manualized transdiagnostic intervention for the treatment of EDs based on cognitive behavioral therapy (CBT). The UP aims to treat emotion regulation deficits, which are argued to be the underlying common factor in all EDs [8]. By focusing on these common mechanisms, the UP offers numerous advantages. For example, it allows the simultaneous treatment of people with different

EDs and comorbid presentations with a single protocol [9] and reduces the costs associated with training mental health professionals [10]. To date, three systematic reviews, which include two meta-analyses, have been conducted to summarize the efficacy of the UP. Overall, these studies reveal that the UP significantly improves anxious and depressive symptoms with moderate to large effect sizes. Additionally, the improvements appear to be maintained over time (up to 3 and 6 months of follow-up) [11-13]. In Spain, a previous clinical trial conducted in the NHS showed that the UP in a group format, compared with treatment as usual, achieved significantly larger improvements in anxious and depressive symptoms, as well as in quality of life at 6-month follow-up [14].

The preferred intervention format by patients with EDs attending the Spanish NHS is individual, face-to-face treatment (85.4%), followed by group (14.2%) and online interventions (0.4%) [15]. These results justify that blended treatments, which use online treatments but maintain some form of individual, face-to-face intervention, could be a potential solution to the availability problems of treatments for EDs in our Spanish NHS. The advantage of blended treatments is that they are dynamic and flexible and they allow using technology to motivate, monitor, give support, and treat patients. Importantly, this is done without losing face-to-face treatment sessions [16,17]. Research has shown that blended interventions are more effective than face-to-face treatments in the reduction of depression and anxiety symptoms [18]. For example, one study found that a blended smartphone treatment, which consisted of four face-to-face sessions and a smartphone app to be used between the sessions, can be as effective as a full behavioural activation treatment in the reduction of major depression. Moreover, comparable scores were also obtained between the two conditions for treatment credibility and working alliance, and therapist time was reduced by an average of 47% in the blended condition [19]. Finally, a recent meta-analysis has also revealed optimistic results regarding the power of blended interventions, given that they allow saving time to the clinicians, in addition to decreasing dropouts and enhancing the maintenance of the benefits obtained with treatment over time [20].

The present study will compare the efficacy and cost-efficiency of the UP in a blended format against traditional, individual, unstructured CBT in a sample of patients with EDs. All the participants will seek treatment at the Spanish NHS. To ensure the generalizability

of the results, our outcomes will be evaluated in several public mental health centres in Spain.

METHODS AND ANALYSIS

Study protocol

The current study is a superiority, multicentre, randomized controlled trial (RCT) with two active conditions: The UP in a blended format (individual UP face to face and UP-APP for Smartphone) and non-structured CBT in an individual format (treatment as usual, TAU). The study is planned to start in January 2022 and end in December 2024.

The expected superiority comes from the fact that the participants in the blended condition will receive additional treatment compared with the TAU condition, which should enhance the benefits of the TAU. In the present investigation, all consecutive patients with EDs attending any of the collaborating centres (see "Sample and recruitment" section) will be asked to participate. It is important to note that this is a feasibility study in which the context and usual procedures of ED management will be kept as naturalistic as possible for implementation purposes. This means that there are some study characteristics that should be bared in mind. For example, some variables will not be predetermined and will only be known at the end of the investigation. This includes, for example, the frequency of the psychological appointments in both conditions (which will vary depending on the patient's evolution and clinician appraisals) or the time spent in the UP-APP by participants in the blended condition (i.e., amount of progress in the treatment modules and exercises). These variables, which might influence on outcomes, will of course be considered in the statistical analysis when the information is available (at the end of the study).

The study was registered on clinicaltrials.gov (NCT04304911). The flow chart of the study design is shown in Figure 1. A schedule of the enrolment, interventions, and assessments is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Table 1).

Sample size

To calculate the required sample size, we used the G*Power software [21]. We obtained a sample size of 129 participants per condition with a 95% power, an alpha coefficient of 0.01, and a conservative effect size of 0.30. Considering a dropout rate of 15% and 5% of candidates who will not meet inclusion criteria, we will recruit at least 155 participants per condition (N=310). The expected effect size and dropout rates come from studies showing that blended interventions lead to lower dropout rates [20] and better outcomes in patients with anxiety and adjustment disorder [18] when compared to face-to-face interventions.

-Insert Fig. 1 around here-

Table 1. Study schedule of enrolment, interventions, and assessments

	STUDY PERIOD						
	Enrolment	**Pre-allocation**	**Allocation**	**Intervention**	**Post-allocation**		
TIMEPOINT	***-t1***	**t_0** **Baseline**	***t_1***	***t_2***	***t_3*** **3 months after the intervention**	***t_4*** **6 months after the intervention**	***t_5*** **12 months after the intervention**
ENROLMENT:							
Eligibility screen	X						
MINI	X				X	X	X
Informed consent	X						
ALLOCATION:		X					
ODSIS		X		X	X	X	X
OASIS		X		X	X	X	X
INTERVENTIONS:							
Treatment as usual				←---→			
UP in blended format				←---→			
OTHER ASSESSMENTS:							
Demographics		X					
MEDI		X			X	X	X
EuroQol-5D		X			X	X	X
FFMQ		X			X	X	X

BEAQ	X			X	X	X
DERS	X			X	X	X
ERQ	X			X	X	X
SUS				X	X	X
CEQ				X	X	X
CSRI				X	X	X
OTS				X	X	X
WAI-S			X			
QALYS	X			X	X	X

Note: *BEAQ,* Brief Experiential Avoidance Questionnaire; *CSRI,* Client Service Receipt Inventory; *CEQ*, Credibility/Expectancy Questionnaire; *DERS,* Difficulties in Emotion Regulation Scale; *ERQ,* Emotion Regulation Questionnaire*; FFMQ,* Five Factor Mindfulness Questionnaire *MEDI,* Multidimensional Emotional Disorder Inventory; *MINI,* Mini International Neuropsychiatric Interview; *OASIS,* Overall Anxiety Severity and Impairment Scale; *ODSIS,* Overall Depression Severity and Impairment Scale; QALYS, Quality-adjusted Life Years; SUS; System Usability Scale; *TOS*, Treatment Opinion Scale; *UP,* Unified Protocol for Transdiagnostic Treatment of Emotional Disorders*; WAI-S,* Working Alliance Inventory-Short

Procedure

UP-APP design (Patient and Public Involvement)

Prior to the design of the UP-APP, our team will conduct two different focus groups, one with patients who already received the UP for their EDs diagnosis and other with therapists trained in the UP intervention. Information about structure, content, format, design, exercises, language, duration, evaluation, feedback, security, adherence, usability, and customization will be collected in the focus groups. Besides, their opinion about the use of Apps and technological devices in clinical psychology and advantages and disadvantages of face-to-face therapy and app-based therapy will be also collected. Some researchers of the study and the engineer's team will participate in these focus groups as observers. The focus groups will be recorded on video to be transcribed by two researchers of the study. The qualitative analysis of the data collected will be used to design the UP-APP for Smartphone. This analysis will consist of generating a system of codes, grouping the he information provided by the participants in the focus groups that referred to the same ideas or highlighting the main ideas.

Sample and recruitment

Participants are individuals over 18 years old, seeking psychological assistance in the Spanish Public Health System. Patients are referred to the study by licensed psychologists, psychiatrists, and clinical psychology residents working at the collaborating centres. Mental health professionals (therapists and psychiatrists from the units to which patients are referred to and who want to collaborate in the study) will be responsible for assessing the current DSM diagnoses (See "Measures" section) and the remaining eligibility criteria (see "Eligibility criteria" section). Individuals with comorbid diagnosis of several EDs are also enrolled in the study.

Recruitment is expected to start in January 2022. The study will be conducted in fifteen different mental health centres of the Spanish NHS, namely: USM Sagasta (Zaragoza), H. Comarcal de Vinaròs (Castellón), Centro San Francisco Javier (Navarra), USM La Milagrosa (Pamplona), Hospital Universitario Reina Sofía de Córdoba, CSM Eguia-Donostia, H. U. de Alicante, CSM del Segrià en Lleida, USM La Fuente de San Luís (Valencia), USM Montoro de Córdoba, H. U. Río Hortega (Valladolid), CSM Mérida, CSM Zafra, USM Fraga y USM Tarazona.

Elegibility criteria

Inclusion and exclusion criteria are described in Table 2.

Table 2. Eligibility criteria

Inclusion criteria	
1	Principal diagnosis of an emotional disorder[a]
2	The patient is over 18 years of age
3	The patient is fluent in the language in which the therapy is performed (Spanish in the present study)
4	The patient has a Smartphone (regardless of the condition, to ensure that the TAU condition does not include more patients that do not have access to a Smartphone)
5	Patients taking pharmacological treatment for their ED will be asked to maintain the same dosages and medications for at least 3 months prior to enrolling in the study and during the whole treatment[b]
6	The patient signs the informed consent form (supplementary file)
Exclusion criteria	
1	The patient presents a severe condition that would require them to be prioritized for treatment. This includes a severe mental disorder (bipolar disorder, personality disorder, schizophrenia, or an organic mental disorder), suicide risk at the time of assessment, or substance use in the last three months
2	The patient has previously received 8 or more sessions of psychological treatment with clear and identifiable CBT principles within the past 5 years

[a]The following disorders will be included based on DSM-5 diagnostic criteria: major depression disorder, dysthymic disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, hypochondria, and adjustment disorders.
Patients with unspecified anxiety disorders and unspecified depressive disorders will also be included as they are frequent in public settings.
[b]If medication stability is not possible, the participant's data will be treated separately in the analyses

Randomization

All consecutive patients with a diagnosis of an ED attending any of the collaborating centres will be asked to participate in the present study. Once the inclusion criteria are met, every patient will be randomly assigned to one of the two experimental conditions: TAU or UP in a blended format. Patients who refuse to participate in the study will receive the TAU outside the RCT. The number of people refusing to participate and the reasons for that decision will be recorded and reported due its interest for future studies. Randomization will be performed by a researcher unrelated to the study using a computer-generated sequence (Randomizer). Randomization will be stratified according to the severity of the primary measures of depression and anxiety, using the cut-off reported in Spanish clinical samples of ED, which has been 10 (0-20) in both scales [22]. This cut-off differentiates patients with moderate-severe symptoms from those with moderate-low symptoms.

Stratification will be made to ensure a comparable proportion of severely depressed and anxious individuals in each group. For each subgroup (i.e., severe or less severe depression and/or anxiety), participants will be randomly assigned to the UP in a blended format or to the TAU.

Therapists and interventions

Participants in both conditions will receive the individual therapy in a face-to-face format. Individuals with an ED also frequently receive pharmacological treatment (i.e., antidepressants and / or anxiolytics) as treatment of choice in the Spanish Mental Health System. The frequency of the appointment sessions with their clinicians will depend on the characteristics of their centres (e.g., existing waiting lists and availability of the clinicians). In addition to these individual face-to-face appointments, participants randomized to the blended condition will be able to use the UP-APP at any time and at whatever pace during the whole duration of the study. Clinicians will recommend participants in the blended condition to work on modules 1, 2, 5, 6 and 8 during at least one week, and modules 3, 4 and 7 during at least two weeks (see the "Unified Protocol in a blended format" section for a detail on the titles of the UP modules).

The relatively naturalistic nature of this study prevents us from defining, prior to the intervention, the exact number of sessions and the time spent in each psychological intervention (TAU vs. UP-blended). This also applies to the time spent by the participants

in the UP-blended condition with the UP-APP. All these variables will be recorded by the UP-APP and the clinicians attending the participants for their inclusion in the statistical analyses.

Previous to start the RCT we will conduct an open pilot study to analyze the preliminary data of the clinical utility and feasibility of the UP-APP in a small sample of patients with emotional disorders diagnosis. Specifically, after the clinical assessment, from those who met the inclusion and exclusion criteria, we will invite 10 patients (in order of date of receipt) to participate voluntarily in this pilot study. Participants will sign the informed consent and data protection. Then, they will be randomized to one baseline condition: 1, 2 and 3 weeks in order of date of receipt (baseline measures will be ODSIS and OASIS [22]). Then patients will receive a face-to-face psychological treatment in a blended format and will receive the instructions to download the UP-APP in their Smartphone. They will be asked to complete a special set of questions to assess the comprehension, appearance, utility, interest, if they would recommend it to other people, usability, intention to use in the future, and satisfaction of the contents of each module of the UP-APP (ad hoc).

For ethical reasons, if a patient feels uncomfortable with the blended format at any time during the study, they will receive the TAU outside the RCT.

Therapists participating in the study will include licensed psychologists with 8 to 20 years of experience in delivering CBT.

Unified protocol in a blended format

For face-to-face interventions, the clinicians in this condition will follow the second edition of the UP therapist manual translated by Osma and Crespo into Spanish [23,24]. As described in detail previously [25] therapists in the UP group received a training workshop on UP prior to the start of the intervention. This consisted of 2 or 3 group workshop sessions in which the therapists were instructed on the delivery of the different UP treatment modules. The duration of the course was between 10 and 20 hours, depending on the availability of the therapists at the centre. In addition to the workshop, all therapists received individual training during 12 therapy sessions through online supervision or participating as a co-therapist with an expert. In both cases, the training was led by the lead author (J.O.), who has been certified as a UP Trainer by the Unified Protocol Institute.

Between sessions, all participants in this condition will have access to the UP-APP. The APP includes the contents of the patient's manual, but using more dynamic and attractive digital material (videos and audios). The UP includes 8 modules: (1) Setting Goals & Maintaining Motivation; (2) Understanding Your Emotions; (3) Mindful Emotion Awareness; (4) Cognitive Flexibility; (5) Countering Emotional Behaviors; (6) Facing Physical Sensations; (7) Emotion exposures, and (8) Moving UP from Here.

In the UP-APP, after completing each module, an assessment of the knowledge acquired will be carried out using true/false questions. The App will collect the correct/incorrect responses and will provide feedback to the participants. Thus, participants will receive positive reinforcement as they progress through the modules and get correct answers to keep them engaged and motivated in the use of the App. In addition, participants will have to complete different exercises throughout the modules, such as records or activities to identify emotion-driven behaviours. They will also be provided with examples of real patients with whom they can identify and which will help them to complete their records. Finally, a weekly assessment will be made to evaluate the evolution of the depression and the anxiety symptoms (ODSIS and OASIS) [22]. The scores over time will be shown to the participants with a graphic display. This weekly evaluation with the APP will also include the participants´ degree of motivation to continue working on the intervention.

Treatment as usual (TAU)

This treatment condition will include individual, non-structured CBT using the following techniques: Psychoeducation, cognitive restructuring, relaxation techniques, mindfulness techniques, exposure techniques, activity scheduling, problem solving and training in communication techniques. This is the treatment of choice by the psychologists at the collaborating Public Mental Health Centres.

Measures

The evaluation protocol is administered by the therapists in a paper and pencil format at the participant's health centre or, when possible, through the Internet using the Qualtrics platform. The assessments will occur in 4 different time points: baseline, 3 months after starting the intervention (t_3), 6 months after starting the intervention (t_4), and 12 months after starting the intervention (t_5). Assessment instruments include demographic

characteristics (age, sex, education, marital status, and work status), a diagnostic interview, and well-established questionnaires for both primary and secondary outcomes. At the end of the study, the clinicians in the TAU condition will complete a self-report sheet describing: the characteristics of their interventions using treatment modules as cues (psychoeducation module, identification of negative thoughts, breathing training, etc.), the average duration of sessions, the number of sessions delivered, the end-of-treatment date, and information on the number of appointments with the psychiatrist and pharmacological treatment prescribed during the study.

Information on the number of appointments with the psychiatrist and the pharmacological treatment prescribed during the study is also collected for patients in the blended condition following the same procedure described for the TAU condition. All the participants using the UP-App will be informed about the data that is going to be registered while using it. Primary and secondary outcomes are described in Table 3.

Table 3. Clinical Outcomes

Instrument	Construct	Reliability (α)	Response range
Primary outcomes			
ODSIS [22,26]	Severity of depressive symptoms	.94	5-point Likert scale ranging from 0 (I didn't feel depressed) to 4 (Constant depression)
OASIS [22,27]	Severity of anxiety symptoms	.87	5-point Likert scale ranging from 0 (I didn't feel anxious) to 4 (Constant anxiety)
MINI [28,29]	Principal diagnosis of ED	NA	Structured diagnostic interview
Secondary outcomes			
		Patient Outcomes	
MEDI [30]	Transdiagnostic dimensions of ED's	NA	9-point Likert response scale ranging from 0 (not characteristic of me/does not apply to me) to 8 (extremely characteristic of me/applies to me very much)
EuroQol-5D [31,32]	Quality of life	NA	5 items ranging from 1 (I do not have problems) to 3 (unable to perform these activities). Thermometer from 0 (worst imaginable health status) to 100 (best imaginable health status)
FFMQ [33,34]	Mindfulness dimensions	.80 to .91	Likert scale ranging from 1 (never or very rarely true) to 5 (very often or always true)
BEAQ [35,36]	Experiential avoidance	.82	6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree)
DERS [37,38]	Emotion regulation	.73 to .93	5-point Likert scale ranging from 1 (never or very rarely) to 5 (very often or always)
ERQ [39,40]	Cognitive Reappraisal and Expressive Suppression		7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree).
		Implementation Outcomes	
SUS [41,42]	Usability	.81	5-point Likert scale ranging from 1 (strong disagreement) to 5 (strong agreement).
CEQ [43,44]	Confidence in the treatment (credibility and client expectancy)	.85	9-point scale rated from 1 (not at all confident) to 9 (very confident).
CSRI [45,46]	Emergency service (total visits), general medical	NA	NA

	inpatient hospital admissions (total days) and outpatient health care services (total visits)		
QALYS [47,48]	Quality-adjusted Life Years	NA	NA
		Patient Satisfaction Outcomes	
WAI-S [49,50]	Working alliance	.91	7-point Likert scale ranging from 1 (never) to 7 (always)
TOS (ad hoc)	Quality of the intervention and its components, discomfort experienced during treatment and the experience of participating in a blended format	NA	4-point Likert scale ranging from 0 (poor or nothing) to 3 (excellent or very much) and 11-point response scale in some items ranging from 0 (nothing) to 10 (very much).
		App Outcomes	
App	Time of use of the App, videos viewed and exercises completed.	NA	NA

Note: BEAQ: Brief Experiential Avoidance Questionnaire; CEQ: Credibility/Expectancy Questionnaire; CSRI: Client Service Receipt Inventory; DERS: Difficulties in Emotion Regulation Scale; ED: Emotional Disorder; ERQ: Emotion Regulation Questionnaire; FFMQ: Five Facet Mindfulness Questionnaire; MEDI: Multidimensional Emotional Disorder Inventory; MINI: Mini-International Neuropsychiatric Interview; NA: Not Applicable; OASIS: Overall Anxiety Severity and Impairment Scale; ODSIS: Overall Depression Severity and Impairment Scale; SUS: The System Usability Scale; TOS: Treatment Opinion Scale.
Scale reliability corresponds to the Cronbach's alpha coefficient *p < .01 **p < .001.

Analyses

For the efficacy analyses, both completers and non-completers (intention-to-treat) analyses will be conducted separately. Then, a baseline comparison of both conditions in all study outcomes will be conducted to ensure that the randomization was successful. Next, mixed, multi-level, linear models will be conducted using the restricted maximum likelihood method to estimate the parameters. All the evaluations from all time points will be used in the models. The models will include covariates if baseline differences are detected. Specifically, the linear mixed model analysis will include the main effects of time (each variable collected at each evaluation time to analyze the evolution over time). The treatment condition and the number of sessions will also be included as interaction effects with time (in order to see differences in the evolution of the variables as a function of the treatment condition and/or as a function of the number of sessions). Finally, the center where the participants have received the treatment will be included as random effects in the model. These analyses will be computed both for the primary and the secondary outcomes. The effect sizes will be computed and interpreted following the Cohen's proposal. Additionally, we will also calculate the Reliable Change Index (RCI) and the Reliable Recovery Index (RRI) to evaluate the effectiveness of both interventions, as proposed by Jacobson and Truax [51].

Missing data will be handled using mixed models, which can be conducted with missing data [52]. For the remaining implementation outcomes (usability, acceptability, and satisfaction) we will compute descriptive analyses. Cost-effectiveness will be calculated by exploring the relationship between the cost of each intervention (cost of TAU or UP in a blended format, number of sessions, medication and use of health resources carried out by the participants [evaluated through the CSRI]) and its consequences in the form of QALYs (standardized health units that allow the quantification of individuals' preferences regarding the quality of life that has been produced by a health intervention [53], the information obtained through the Euroqol allows the calculation of QALYs). Other measures of intervention penetration will be used, such as the number of consumers who were eligible or willing to use the app (end users). All analyses will be conducted with SPSS v24.0 [54] and Mplus v8.0 [55]. The study will follow the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) recommendations [56].

ETHICS

This study will be carried out in accordance with the study protocol, the Helsinki Declaration, and good clinical practice. This superiority, multicentre, RCT is currently under an approval process by the ethical and research committees of all the collaborating centres. It has already been approved by Ethics Research Committee of Navarra, Castellón, Euskadi, Castilla y León, Extremadura, Lleida and Aragón.

Data handling will be carried out according to the premises established by Spanish laws [57]. The security and confidentiality of the participants' data are guaranteed by using alphanumeric codes (SUP001) instead of names. In addition, the demographic data will be hold separately from the rest of the data and will only be available to the researchers responsible for the data. The right to privacy will be a priority. The data obtained with the UP-APP will also comply with the mentioned guidelines. We will follow the necessary technical measures to ensure data safety and confidentiality, such as information encryption, access control and protection, security copies, updating of the operating system, security patches, centralized management of passwords, roles, users and privileges, patches management, and vulnerabilities detection. Outcomes will be disseminated through publication in peer-reviewed journals and presentations at international conference meetings. In addition, we will give visibility to the results through www.researchgate.net, https://clinicaltrials.gov/ and the website of our research group.

Author contributions

JO: Conceptualization, funding acquisition, project administration, supervision, writing-original draft. LMG: Conceptualization, investigation, visualization, writing-original draft. OPB: Conceptualization, investigation, methodology, writing – review, and editing. MVNH: Conceptualization, writing - review and editing. AGP: Methodology, software, writing – review, and editing. CSR: Conceptualization, methodology, writing – review, and editing.

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Competing interests

None declared.

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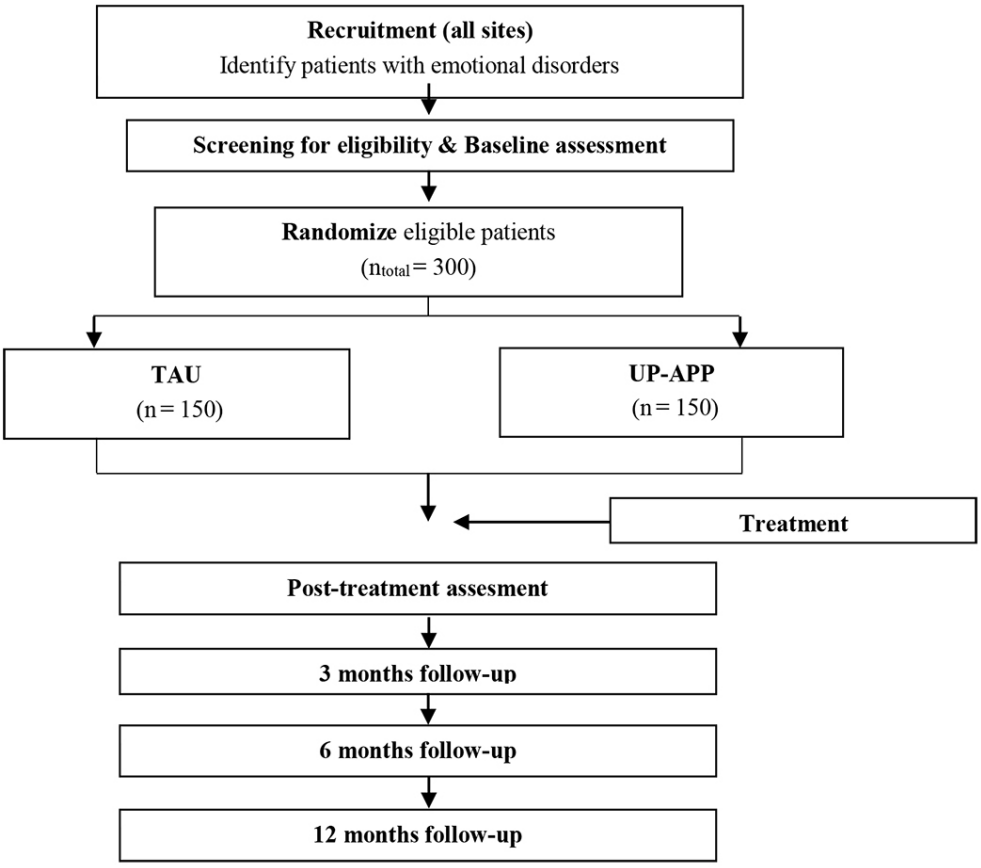
Figure 1. Study Flow Chart

Fig. 1 Study flow chart



90x90mm (300 x 300 DPI)

Supplementary material. Patient Informed Consent

PATIENT INFORMED CONSENT

PROJECT TITLE: Study of the implementation, efficacy and cost-effectiveness of the Unified Protocol in hybrid format for the transdiagnostic treatment of emotional disorders in the Spanish NHS (PI20/00697)

PRINCIPAL INVESTIGATOR: <<name and surname of the principal investigator>>

Centre/Hospital: <<name of the Mental Health Centre>>

FUNDING ENTITY: Study funded by the Ministry of Science and Innovation, Instituto de Salud Carlos III for Health Research Projects of the 2020 call of the Strategic Action in Health 2017-2020 (code PI20/00697).

GENERAL DESCRIPTION: We are writing to inform you about a research study in which you are invited to participate and which has been approved by the <<name of the Drug Research Ethics Committee of the Hospital>>. Considering that you suffer from an Emotional Disorder (mood or anxiety disorder), we are asking for your consent to participate in a study about which we inform you below. Before deciding whether or not you want to participate, please read this document carefully, which includes information about this project. You can ask any questions you may have and ask for clarification on any aspect of the study.

PURPOSE OF THE STUDY: We are contacting you to request your collaboration in the research project entitled: "Study of implementation, efficacy and cost-effectiveness of the Unified Protocol in hybrid format for the transdiagnostic treatment of emotional disorders in the Spanish NHS". Our objective with this research is to analyse the efficacy and cost-effectiveness of a transdiagnostic psychological treatment applied in a hybrid format (face-to-face treatment + mobile App), with the aim of providing a resource that allows working and training skills in the period between face-to-face appointments. To do this, a randomly selected group of users of a Mental Health Unit will receive the usual psychological treatment at the centre, and another group will receive the treatment in hybrid format (face-to-face treatment + mobile App).

EXPLANATION OF THE STUDY: Through a randomisation system, participants will be assigned to one or other of the following treatment modalities:

- Usual psychological treatment modality of the centre (individual and face-to-face format).
- Hybrid treatment modality (individual and face-to-face treatment + mobile App).

Study activities - Usual psychological treatment condition of the centre

The following is the procedure and activities that you will carry out in this treatment modality:

1. An initial psychological assessment will be carried out (by means of structured diagnostic clinical interview). The results of the assessment will be part of a database of participants. The estimated duration is between 20-30 minutes.

Supplementary material. Patient Informed Consent

2. Pre-intervention assessment: Before starting the psychological intervention, you will have to complete the full assessment protocol. This consists of a series of questionnaires and is estimated to take between 30-45 minutes to complete.
3. Usual treatment: Psychological intervention following the usual treatment used in your health centre. You will have a psychologist assigned to you from your Mental Health Centre, who will be in charge of making individual appointments and offering you the psychological treatment he/she considers appropriate according to your psychological needs.
4. Follow-up evaluations at 3, 6 and 12 months after starting the intervention: the complete evaluation protocol will be administered again during the follow-ups that will take place at 3, 6 and 12 months after starting the psychological intervention (estimated duration to fill them in is between 30-45 minutes).

Study activities - Hybrid treatment condition (individual and face-to-face treatment + mobile App).

Below, we present the procedure and activities that you will carry out in the event that you agree to participate in this project and are assigned through the randomisation system to the hybrid treatment condition (face-to-face treatment + mobile App):

5. An initial psychological assessment (by means of a structured clinical diagnostic interview) will be carried out. The results of the assessment will be part of a database of participants. The estimated duration is between 20-30 minutes.
6. Pre-intervention assessment: Before starting the psychological intervention, you will complete the full assessment protocol consisting of a series of questionnaires, estimated to take between 30-45 minutes to complete.
7. Psychological Treatment based on the Unified Protocol + App: Transdiagnostic cognitive-behavioural treatment applied in a hybrid format (face-to-face treatment + App). To ensure that all participants receive the same intervention, therapists will use the Unified Protocol Manual (Barlow et al., 2018a). This Protocol consists of 8 treatment modules (Table 2). The duration and frequency of individual sessions will be determined by the clinical psychologist according to their availability and schedule. The treatment modules content is shown in Table 2.

Table 2. Treatment modules and content

Module 1	Setting Goals & Maintaining Motivation
Module 2	Understanding your emotions
Module 3	Mindful Emotion Awareness
Module 4	Cognitive flexibility
Module 5	Countering Emotional Behaviors
Module 6	Facing Physical Sensations
Module 7	Emotion exposures

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Module 8	Moving UP from here

8. Follow-up assessments at 3, 6 and 12 months after starting the intervention: the complete assessment protocol will be administered again during the follow-ups that will take place 3, 6 and 12 months after starting the psychological intervention (estimated time to complete them is between 30-45 minutes).

RISKS AND DISCOMFORTS OF PARTICIPATING IN THE STUDY

Both treatment modalities have demonstrated their efficacy and the benefit to be obtained with this study is to improve the efficiency of psychological treatments for the treatment of people with emotional disorders. In addition, there are no risks associated with participation in this research.

BENEFIT AND MEDICAL CARE

It is likely that you will not receive any personal benefit from your participation in this study. However, the data collected in this study may lead to increased knowledge about emotional disorders.

VOLUNTARY PARTICIPATION

Your participation in this study is completely voluntary: If you decide not to participate, you will receive all the medical care you may need and your relationship with the medical team caring for you will not be affected.

DATA PROCESSING AND CONFIDENTIALITY

Your consent is requested for the use of your data for the development of this project. Both personal data (age, sex, race) and health data will be collected using a coding procedure. Only your therapist and the main researcher at the centre, will be able to relate this data to you, being responsible for keeping all data you provide. The information will be processed during the analysis of the results obtained and will appear in the final reports. In no case will it be possible to identify you, guaranteeing the confidentiality of the information obtained, in compliance with current legislation.

The study complies with the provisions of Organic Law 3/2018, of 5 December, on the protection of personal data and the guarantee of digital rights, which repeals Organic Law 15/1999, of 5 December, on the protection of personal data. Also complies with the European Parliament Regulation 2016/679 of personal data protection, the Helsinki Declaration (Seul, 2008) and the Biomedic Research Law 14/2007.

Personal data will be processed by <<name and surname of the principal investigator>>. No data will be passed on to third parties, unless legally obliged to do so. You will be informed that you have the right to access, rectify, delete, limit or oppose the processing of your data.

Access to your identified personal information will be restricted to the study doctor/collaborators, health authorities (Spanish Agency of Medicines and Health Products, foreign health authorities), the Research Ethics Committee and personnel authorised by the sponsor (study monitors, auditors), when required to check the study data and procedures, but always maintaining their confidentiality in accordance with current legislation.

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The data will be collected in a research file under the responsibility of the institution and will be processed in the framework of its participation in this study.

The promoter will adopt the appropriate measures to guarantee the protection of your privacy and will not allow your data to be cross-referenced with other databases that could allow you to be identified.

In accordance with data protection legislation, you may exercise your rights of access, modification, objection and deletion of data by contacting your psychologist.

REVOCATION OF CONSENT

You may revoke your participation at any time without explanation. In this case, no new data will be collected after you leave the study.

If you have any questions you can ask your psychologist now or later, even after the study has begun. If you wish to ask questions later, you can contact the person in charge of the research: blind note

Thank you very much for your attention.

Supplementary material. Patient Informed Consent

INFORMED CONSENT FORM

PROJECT TITLE: Study of the implementation, efficacy and cost-effectiveness of the Unified Protocol in hybrid format for the transdiagnostic treatment of emotional disorders in the Spanish NHS (PI20/00697)

PRINCIPAL INVESTIGATOR: <<name and surname of the principal investigator>>

Centre/Hospital: <<name of the Mental Health Centre>>

FUNDING ENTITY: Study funded by the Ministry of Science and Innovation, Instituto de Salud Carlos III for Health Research Projects of the 2020 call of the Strategic Action in Health 2017-2020 (code PI20/00697).

I, <<name and surname of the participant>>

□ I have read the information sheet I have been given about the study.

□ I have been able to ask questions about the study.

□ I have received sufficient information about the study.

□ I have spoken to <<name and surname of the Psychologist>>.

□ I understand that my participation is voluntary.

□ I understand that I can withdraw from the study:

- Whenever I want.
- Without having to explain myself.
- Without affecting my medical care.

I will receive a signed and dated copy of this informed consent document.

I freely give my agreement to participate in the study.

Signature of the legal representative, family member or de facto related person	Signature of the researcher/Psychologists

Date:

I wish to be informed of information derived from the research that may be relevant to my health:

☐ YES

☐ NO

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1, 4.
	2b	All items from the World Health Organization Trial Registration Data Set	Not reported
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	Tittle page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not Applicable
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2,3
	6b	Explanation for choice of comparators	2,3
Objectives	7	Specific objectives or hypotheses	3

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10, 11, 12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11, 12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not reported
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10, 11, 12

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12, 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12, 13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12, 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not applicable
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not reported
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not reported
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not reported
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.